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Tetrahedron Letters 44 (2003) 331–334

TETRAHEDRON LETTERS

New and efficient method for esterification of carboxylic acids with simple primary and secondary alcohols using cerium(IV) ammonium nitrate (CAN)

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Received 3 September 2002; revised 31 October 2002; accepted 8 November 2002

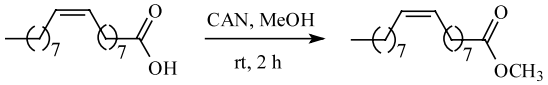
Abstract—The esterification of phenylacetic acids and *cis*-oleic acid with primary and secondary simple alcohols, which also act as solvents using cerium(IV) ammonium nitrate (CAN) at room temperature gave phenylacetates and methyl (9*Z*)-octadec-9-enoate. The reactions, which occur under relatively mild conditions, afforded the desired products in good to excellent yields.

Esterification of carboxylic acids with alcohols has been recognized as one of the most important unit reactions due to the wide utility of esters in organic, bioorganic, and related fine-chemical synthesis.[1] There are many methods for esterification using specific dehydrating reagents under mild liquid-phase conditions: DCC,[2] halopyridinium salts,[3] 2,4,6-trichlorobenzoyl chloride,[4] *N*,*N*-carbonyldiimidazole,[5] BOP-Cl,[6] DPC,[7] DPTC,[8] DPAT,[9] dimethylsulfamoyl chloride/dimethylamine,[10] and several other condensation agents.[11] Now, we disclose a new method for the esterification of carboxylic acids with alcohols using cerium(IV) ammonium nitrate (CAN) under mild conditions.

CAN has been widely used in carbon–carbon bond-forming reactions via radicals.[12] In addition, it also has been applied in carbon-hetero atom bond formation. Trahanovsky and Robbins reported the CAN-mediated addition of azide to styrene as early as 1971[13] and subsequent use of the reaction in the synthesis of aminosugars was reported by Lemieux et al.[14] Very recently Nair et al. have reported the thiocyanation of styrenes and indoles using NH_4SCN and CAN.[15,16] Nair et al. have also reported the conversion of cinnamates to α-azidocinnamates, cinnamic acids to β-azido styrenes[17] and styrenes to phenacyl azides and phenacyl thiocyanates.[18] However, to our knowledge, the esterification of carboxylic acids using CAN has never been reported. We have undertaken an investigation of the reactions of various phenylacetic acids and *cis*-oleic acid with simple alcohols using CAN. Phenylacetic acid and its derivatives possess growth regulator activity on pre-germinated tomato seedlings.[19] Our results indicating the usefulness of the process are presented here.

The esterification reactions were first studied using *cis*-oleic acid **1** and methanol. CAN (2.3 mmol) was added to a solution of **1** (1.6 mmol) in dry methanol (10 mL) and stirred at room temperature for 2 h. The solvent was evaporated in vacuo. The residue was diluted with saturated aqueous NaCl solution and extracted with EtOAc (3×15 mL). The extracts were dried over anhydrous $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography to give **2** in 99% yield as a colorless liquid (Scheme 1).

When CAN was not used in this reaction, no reaction took place and most of the starting material was recovered. We also examined the reaction using a catalytic amount of CAN. When 1 mol% and 5 mol% of CAN was used in this reaction, product **2** was obtained in only 25 and 30% yields, respectively. Therefore, an equivalent amount of CAN is necessary to carry out the



1 **2** (99%)

Scheme 1.

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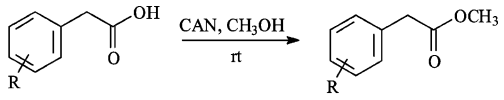
PII: S0040-4039(02)02578-9

Table 1. Esterification of phenylacetic acids with methanol using CAN



3a-j **4a-j**

Entry	Substrate	R	Time (h)	Products	Yields (%)*
1	**3a**	H	12	**4a**	76
2	**3b**	2-Br	12	**4b**	98
3	**3c**	3-Br	12	**4c**	99
4	**3d**	4-Br	12	**4d**	93
5	**3e**	2-Cl	12	**4e**	99
6	**3f**	3-Cl	12	**4f**	98
7	**3g**	4-Cl	12	**4g**	92
8	**3h**	2-OMe	6	**4h**	87
9	**3i**	3-OMe	6	**4i**	82
10	**3j**	2-NO_2	24	**4j**	70

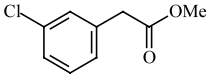
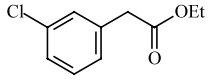
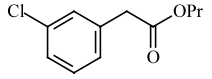
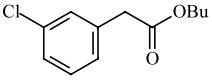
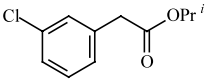
* Isolated yield.

reaction to completion. Various carboxylic acids were treated with methanol using CAN to give the corresponding methyl esters.[20] The results are summarized in Table 1. Several functionalities present in the carboxylic acids such as a double bond, a halogen, a methoxy group, and a nitro group were tolerated. In all the cases the corresponding methyl esters were obtained in good to excellent yields. Phenylacetic acid **3a** gave the corresponding methyl 2-phenylacetate **4a** in 76% yield (entry 1). 2-(2-Bromophenyl)acetic acid **3b**, 2-(3-bromophenyl)acetic acid **3c**, and 2-(4-bromophenyl)acetic acid **3d** afforded the corresponding methyl acetates **4b**,[21] **4c** and **4d** in 98, 99 and 93% yields, respectively (entries 2–4). 2-(2-Chlorophenyl)acetic acid **3e**, 2-(3-chlorophenyl)acetic acid **3f**, and 2-(4-chlorophenyl)acetic acid **3g** afforded the corresponding methyl acetates **4e**, **4f** and **4g** in 99, 98 and 92% yields, respectively (entries 5, 6, and 7). 2-(2-Methoxyphenyl)acetic acid **3h** and 2-(3-methoxyphenyl)acetic acid **3i** provided the corresponding methyl 2-(2-methoxyphenyl)acetate **4h** and methyl 2-(3-methoxyphenyl)acetate **4i** in 87 and 82% yields, respectively (entries 8 and 9). In these two cases, we observed small amounts of by-products, however they were not identified. 2-(2-Nitrophenyl)acetic acid **3j** has also been examined in this reaction, the reaction was much slower and required 24 h to give the product **4j** in 70% yield (entry 10),[22] which indicated that the 2-nitro group decreases the rate of formation of the corresponding ester.

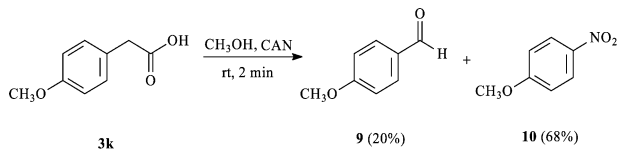
In order to examine the reactivity of alcohols in this reaction, 3-chlorophenyl acetic acid **3f** was reacted with various primary, secondary, and tertiary alcohols using CAN. The results are summarized in Table 2. The reactions of ethanol, *n*-propanol, and *n*-butanol with **3f** gave the corresponding acetates **5**, **6** and **7** in 99% yields, respectively (entries 2–4).[23] Isopropanol afforded isopropyl-2-(3-chlorophenyl)acetate **8** in 70% yield and 24 h (entry 5),[21] which indicated that relatively sterically crowded secondary alcohols required an increased reaction time and with a lower yield compared to the primary alcohols. Unfortunately, the sterically crowded *tert*-butanol did not undergo this esterification reaction even when the temperature was increased up to 70°C (entries 6 and 7).

It was of interest to probe the chemoselectivity of the CAN-mediated esterification reaction. When 4-methoxy-phenylacetic acid **3k** was treated with methanol and CAN under the typical conditions, the

Table 2. Esterification of 3-chlorophenylacetic acid with alcohols using CAN

Entry	Alcohols	Conditions	Product	Yield (%)*
1	MeOH	CAN, rt, 12 h	 **4f**	98
2	EtOH	CAN, rt, 12 h	 **5**	99
3	*n*-PrOH	CAN, rt, 12 h	 **6**	99
4	*n*-BuOH	CAN, rt, 12 h	 **7**	99
5	*i*-PrOH	CAN, rt, 24 h	 **8**	70
6	*t*-BuOH	CAN, rt, 12 h	no reaction	-
7	*t*-BuOH	CAN, 70°C, 24 h	no reaction	-

* Isolated yield.



Scheme 2.

reaction took place much faster requiring only 2 min. In the event, no esterification occurred, instead resulting in the formation of 4-methoxybenzaldehyde **9** and 1-methoxy-4-nitrobenzene **10** in 20 and 68% yields, respectively (Scheme 2).[24,25]

In conclusion, we have explored a facile and efficient route for the esterification reaction between aliphatic and aromatic carboxylic acids and simple primary or secondary alcohols, (which also act as solvents) using cerium(IV) ammonium nitrate. This method did not necessitate the use of a dehydrating reagent and/or the azeotropic removal of water. Evidently, the present procedure appears attractive for its operational simplicity, and generally high yields of products.

Acknowledgements

We thank the National Science Council of the Republic of China for financial support of this program.

References

1. (a) Beaz, G. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 6, p. 323; (b) Franklin A. S. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2451 and **1999**, 3537; (c) Otera, J. *Chem. Rev*. **1993**, *93*, 1449; (d) Greene, T. W.; Wuts, P. G. In *Protective Groups in Organic Synthesis*; 3rd ed.; Wiley-Interscience: New York, 1999; p. 372.
2. (a) Ziegler, F. E.; Berger, G. D. *Synth. Commun*. **1979**, *9*, 539; (b) Hassner, A.; Alexanian, V. *Tetrahedron Lett*. **1978**, *19*, 4475.
3. (a) Mukaiyama, T. *Angew. Chem., Int. Ed. Engl*. **1979**, *18*, 707; (b) Saigo, K.; Usui, M.; Kikuchi, K.; Shimada, E.; Mukaiyama, T. *Bull. Chem. Soc. Jpn*. **1977**, *50*, 1863.
4. Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn*. **1977**, *52*, 1989.
5. (a) Ohta, S.; Shimabayashi, A.; Aono, M.; Okamoto, M. *Synthesis* **1982**, 833; (b) Staab, H. A. *Angew. Chem., Int. Ed. Engl*. **1962**, *1*, 351.
6. Meseguer, J. D.; Coll, A. L. P.; Lizarbe, J. R. F.; Bilbao, A. Z. *Synthesis* **1980**, 547.
7. (a) Denis, J. N.; Greene, A. E. *J. Am. Chem. Soc*. **1988**, *110*, 5917; (b) Kim, S.; Lee, J. I.; Ko, Y. K. *Tetrahedron Lett*. **1984**, *25*, 4943.
8. Saitoh, K.; Shiina, I.; Mukaiyama, T. *Chem. Lett*. **1998**, 679.
9. Wakasugi, K.; Misaki, T.; Yamada, K.; Tanabe, Y. *Tetrahedron Lett*. **2000**, *41*, 5249.
10. Wakasugi, K.; Nakamura, A.; Tanabe, Y. *Tetrahedron Lett*. **2001**, *42*, 7427.
11. See e.g.: (a) Zacharie, B.; Connolly, T. P.; Penney, C. L. *J. Org. Chem*. **1995**, *60*, 7072; (b) Vedejs, E.; Daugulis, O. *J. Org. Chem*. **1996**, *61*, 5702; (c) Wright, S. W.; Hageman, D. L.; McClure, L. D. *Tetrahedron Lett*. **1997**, *38*, 7345; (d) Thierry, J.; Yue, C.; Potier, P. *Tetrahedron Lett*. **1998**, *39*, 1557.
12. Nair, V.; Mathew, J.; Prabhakaran *Chem. Soc. Rev*. **1997**, 127.
13. Trahanovsky, W. S.; Robbins, M. D. *J. Am. Chem. Soc*. **1971**, *93*, 5256.
14. Lumieux, R. V.; Ratchiffe, R. M. *Can. J. Chem*. **1979**, *57*, 1244.
15. Nair, V.; Nair, L. G. *Tetrahedron Lett*. **1998**, *39*, 4585.
16. Nair, V.; George, T. G.; Nair, L. G.; Panicker, S. B. *Tetrahedron Lett*. **1999**, *40*, 1195.
17. Nair, V.; George, T. G. *Tetrahedron Lett*. **2000**, *41*, 3199.
18. Nair, V.; Nair, L. G.; George, T. G.; Augustine, A. *Tetrahedron* **2000**, *56*, 7607.
19. Iacobellis, N. S.; De Vay, J. E. *Physiol. Plant. Pathol*. **1987**, *30*, 421.
20. Spectral data of: compound **4c** (colorless liquid): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.43–7.35 (m, 2H), 7.21–7.12 (m, 2H), 3.68 (s, 3H), 3.57 (s, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 171.0, 135.9, 132.1, 130.0, 129.8, 127.8, 122.3, 51.9, 40.4; EI–MS m/z 230 ($(M+1)^+$, 11), 228 ($(M-1)^+$, 11), 171 (55), 169 (55), 105 (55), 89 (100). **4d** (colorless liquid): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.47 (d, 2H, $J=8.6$ Hz), 7.19 (d, 2H, $J=8.6$ Hz), 3.72 (s, 3H), 3.63 (s, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 171.5, 132.5, 131.2, 130.7, 120.6, 51.7, 39.9; EI-MS m/z 230 ($(M+1)^+$, 58), 228 ($(M-1)^+$, 58), 171 (91), 169 (100), 89 (38). **4e** (colorless liquid): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.34–7.16 (m, 4H), 3.76 (s, 2H), 3.67 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.6, 134.2, 132.1, 131.2, 129.2, 128.4, 126.6, 51.7, 38.6; EI-MS m/z 186 ($(M+2)^+$, 3), 184 (M^+, 7), 149 (74), 125 (100). **4f** (colorless liquid): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.27 (s, 1H), 7.23–7.11 (m, 3H), 3.66 (s, 3H), 3.57 (s, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 171.0, 135.7, 134.0, 129.5, 129.2, 127.3, 127.1, 51.8, 40.3; EI-MS m/z 186 ($(M+2)^+$, 5), 184 (M^+, 15), 127 (31), 125 (100), 105 (28), 89 (57). **4g** (colorless liquid): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.26 (dd, 2H, $J=8.6$ Hz), 7.17 (dd, 2H, $J=8.6$ Hz), 3.65 (s, 3H), 3.56 (s, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 171.0, 132.7, 132.3, 130.4, 128.4, 51.7, 40.1; EI-MS m/z 186 ($(M+2)^+$, 8), 184 (M^+, 16), 127 (28), 125 (100), 89 (44). **4h** (colorless liquid): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.31–7.17 (m, 2H), 6.97–6.86 (m, 2H), 3.82 (s, 3H), 3.69 (s, 3H), 3.65 (s, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 172.1, 157.4, 130.7, 128.4, 122.9, 120.4, 110.4, 55.3, 51.7, 35.6; EI-MS m/z 180 (M^+, 24), 121 (65), 91 (100). **4i** (colorless liquid): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.24 (t, 1H, $J=8.4$ Hz), 6.85 (s, 1H), 6.89–6.79 (m, 2H), 3.79 (s, 3H), 3.69 (s, 3H), 3.61 (s, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 171.6, 159.6, 135.2, 129.3, 121.4, 114.7, 112.4, 54.9, 51.7, 40.9; EI-MS m/z 180 (M^+, 37), 121 (100), 91 (36), 77 (38).
21. Beckwith, A. L. J.; Gerba, S. *Aust. J. Chem*. **1992**, *45*, 289.
22. Salerno, C. P.; Magde, D.; Patron, A. P. *J. Org. Chem*. **2000**, *65*, 3971.

23. Spectral data of: Compound **5** (colorless liquid): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.28 (s, 1H), 7.25–7.21 (m, 2H), 7.16 (m, 1H), 4.15 (q, 2H, $J=7.2$ Hz), 3.57 (s, 2H), 1.24 (t, 3H, $J=7.2$ Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.6, 135.9, 134.0, 129.5, 129.2, 127.3, 127.0, 60.8, 40.6, 13.9; EI-MS m/z 200 ($(M+2)^+$, 10), 198 (M^+, 29), 125 (100), 119 (21), 89 (29). **6** (colorless liquid): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.28 (s, 1H), 7.23–7.20 (m, 2H), 7.16 (m, 1H), 4.04 (t, 2H, $J=7.2$ Hz), 3.57 (s, 2H), 1.63 (sext., 2H, $J=7.2$ Hz), 0.90 (t, 3H, $J=7.2$ Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.6, 135.9, 134.0, 129.5, 129.2, 127.2, 127.0, 66.3, 40.6, 21.7, 10.0; EI-MS m/z 214 ($(M+2)^+$, 3), 212 (M^+, 9), 170 (11), 125 (100), 89 (85). **7** (colorless liquid): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.27 (s, 1H), 7.24–7.20 (m, 2H), 7.17 (m, 1H), 4.09 (t, 2H, $J=6.6$ Hz), 3.57 (s, 2H), 1.57 (quint., 2H, $J=7.2$ Hz), 1.33 (sext., 2H, $J=7.2$ Hz), 0.90 (t, 3H, $J=7.2$ Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.8, 135.7, 133.9, 129.3, 129.0, 127.1, 126.8, 64.6, 40.5, 30.2, 18.6, 13.1; EI-MS m/z 228 ($(M+2)^+$, 5), 226 (M^+, 12), 170 (100), 125 (69), 91(57). **8** (colorless liquid): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.29 (s, 1H), 7.24–7.22 (m, 2H), 7.17 (m, 1H), 5.02 (sept., 1H, $J=6.4$ Hz), 3.55 (s, 2H), 1.24 (s, 3H), 1.21 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.3, 136.1, 134.2, 129.6, 129.3, 127.3, 127.1, 68.4, 41.1, 21.6, 21.6; EI-MS m/z 214 ($(M+2)^+$, 11), 212 (M^+, 30), 127 (36), 125 (100), 91 (43), 89 (36).
24. Ali, M. H.; Wiggin, C. J. *Synth. Commun.* **2001**, *31*, 1389.
25. Spectral data of: Compound **10** (colorless solid): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.20 (d, 2H, $J=9.4$ Hz), 6.91 (d, 2H, $J=9.4$ Hz), 3.91 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 164.6, 141.6, 125.9, 114.0, 55.9; EI-MS m/z 153 (M^+, 72), 123 (100), 95 (43).